The Paradox of Androgens and Balding: Where Are We Now?

Investigating the role that androgens play in regulating the pilosebaceous unit is critical to our understanding of the pathogenesis of acne, hirsutism, and balding. In the past decade there have been very few in vitro studies of androgen metabolism in human sebocytes or hair follicles, primarily because of technical considerations [1–3]. It is now widely accepted that androgens are at least permissive if not necessary for sebocyte stimulation in acne, for the growth of secondary sexual hair, and paradoxically for the regression of hair growth in the balding scalp. This paradox of androgen regulation of hair growth is not understood at all: The same androgenic stimulus enhances growth and differentiation to terminal hair in certain target areas such as the axilla, mons pubis, and beard, and causes regression from terminal to vellus hair in the frontal, temporal, and crown regions of the scalp in genetically susceptible individuals. To explain such phenomena, the target end organ, i.e., the pilosebaceous unit, needs to be studied.

The paper by Sawaya et al in this issue presents another step toward understanding the differences in metabolism between "balding" and "hairy" scalp skin. In 1974, Schweikert and Wilson [4,5] studied metabolism of labeled testosterone and androstenedione in individual hair roots from balding and hairy scalp areas and, in general, found a higher formation of 5α-reduced metabolites and 17-ketosteroid metabolites in balding men. However, it was never clear whether these changes were primary or secondary to the balding process. A few studies on skin homogenates have been published [6–9], but only a little work has been done to study isolated hair follicles or sebocytes comparing different anatomic locations or physiologic states. The current paper has used a relatively straightforward in vitro technique for isolating sebocytes from small tissue samples of scalp skin obtained either during hair transplantation or at autopsy. Specifically, Sawaya et al have shown that the enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD), which converts dehydroepiandrosterone (DHA) to Δ4-androstenedione (Ad) as well as androstanedione to testosterone (T) (Fig 1), has greater activity in balding than in hairy scalp samples. They added the precursor androgen [^{3}H]DHA to isolated sebocytes and measured the amounts of more potent androgenic metabolites, [^{3}H]A and [^{3}H]T, which were produced. Furthermore, they showed that this dichotomy of activity was mirrored in the specific 3β-HSD activity of the cytosolic fraction of sebocyte homogenates. Oddly, although the microsomal fraction possessed the highest specific activity of 3β-HSD, there was no difference between hairy and balding scalp in this fraction! In previous studies comparing acne prone and acne free skin [8], it was never firmly established whether increased androgen metabolic activity was simply due to the presence of a greater number of sebocytes or whether the sebocytes had higher specific activity. Sawaya et al have overcome this problem with the painstaking but rewarding use of isolated sebocytes, thus enabling them to compare specific activity per milligram of protein. Unfortunately the "chicken-egg" dilemma of whether the differences they observed in androgen metabolism between balding and hairy scalp was a cause or a result of the balding process still remains unsolved.

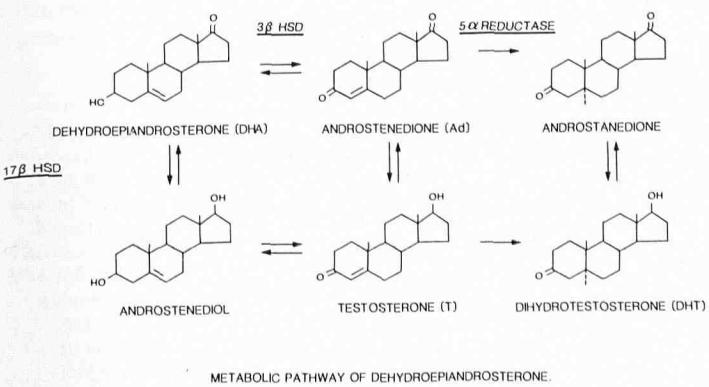

Figure 1. Part of the metabolic pathway of steroid hormone metabolism in the skin. Dehydroepiandrosterone (DHA) can be metabolized to more potent androgens such as testosterone (T) and dihydrotestosterone (DHT).

The work by Sawaya et al has also emphasized that sebocytes are perfectly capable of metabolizing the so-called "weak" androgen, DHA, to much more potent metabolites such as T. DHA itself is a product primarily of the adrenal gland and its effect has often been disregarded clinically because it is intrinsically such a weak androgen. The fact that the skin can convert DHA to T has been documented before [1,2,7–13]. However, these studies confirming the ability of human scalp skin to metabolize DHA to other potent metabolites and showing differences between balding and hairy skin should make us more aware of the potential role elevated or even high-normal amounts of circulating DHA may play in balding.

It is hoped that this study will stimulate other workers to pursue some of the many unanswered questions relating to end organ metabolism of androgens in the skin. There are certainly more mysteries than facts in this area. For example, we still do not know in which cell types, keratinoctyes, fibroblasts, sebocytes, or hair follicle components, the androgen receptors are located; nor do we know which cells in the skin possess the enzymes necessary to metabolize such androgens. Even within the pilosebaceous unit, we cannot with certainty extrapolate results obtained from the sebaceous gland directly to growth or differentiation of the hair follicle. It is well established that there are androgen receptors in sebocytes [14,15]; however, it has been much more difficult to firmly localize such receptors and/or enzymatic systems in the hair follicle. There are virtually no data localizing androgen receptors or enzyme systems to specific cell types within the hair follicle.

It is by trying to understand the mode of action of androgens in the hair follicle that we may finally decipher what causes androgens to paradoxically stimulate hair growth in secondary sexual areas and balding on the scalp. We look forward to further studies of androgen metabolism of the pilosebaceous unit which may define other enzyme activities (17β HSD, 5α-reductase or aromatase, for example) and/or androgen receptor activity in homogenous cell types from various anatomic or physiologic locations.

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